

I know, the only available compound of this group which would exert its actions unaltered is the new one, synephrin.

Attempts to avoid the toxicity of the cocaine-epinephrin combination, used in the nose and throat, by substituting some of the other vaso-constrictors is also unpromising, since the local vaso-constrictor power of ephedrin and phenylaminoethanol in the nose is lost in the presence of cocaine,¹⁰ just as it is on systemic administration. Similarly, the asthmatic type of reaction in cocaine poisoning could not be adequately treated with ephedrin, since cocaine antagonizes bronchial muscle responses as well.

Thus, it is seen that what was originally only an interesting pharmacological experiment has important fundamental bearings on the exact determination of the seat of action of the so-called "sympathomimetic" amines, and also strong clinical implications.

CONCLUSIONS

1. Cocaine, but not procaine, butyn and saligenin, injected subcutaneously in doses (5 to 15 milligrams per kilo) corresponding to those used in infiltration anesthesia, profoundly modifies the circulatory responses to epinephrin, ephedrin, and related drugs.

2. The modifications consist of sensitization, desensitization, or complete abolition, of the circulatory responses (blood pressure and heart rate), according to the drug used.

3. Cocaine also modifies the responses of the blood vessels (nose, etc.) to vasoconstrictor drugs after local application, and of the bronchi to bronchodilator agents used systemically.

4. These phenomena are possible whenever cocaine is absorbed, even in otherwise ineffective doses, and are of importance in the systemic reactions of cocaine poisoning, and in treating accidents of local anesthesia.

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AGRANULOCYTIC ANGINA*

REPORT OF CASE

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AGRANULOCYTIC angina is an acute systemic disease of unknown etiology, characterized anatomically by leukopenia, a pronounced reduction or total absence of granular leukocytes in the blood and hematopoietic organs, and an ulcerative or gangrenous inflammation of the buccopharyngeal membranes; clinically by hyperpyrexia, asthenia, and, commonly, an early fatal termination.

HISTORY AND LITERATURE

If we look back upon the literature of former decades, we find as early as 1880 that anginas were mentioned which were marked by the necrotic character of the pharyngeal tonsils and their surrounding tissues, and which terminated fatally for the patients. These anginas were differentiated from diphtheria even at that time. We are reminded of case reports by Wheat in 1885, Cohn in 1893, Noltenius in 1900, Schwarz in 1904, Turk in 1907, and Marchand in 1913, which presented pictures which today are recognized as agranulocytic angina.

It was not, however, until November 1922 when Werner Schultz presented his series of five cases in considerable detail, designating the disease as agranulocytosis, that the medical profession became conscious of the presence of a new clinical syndrome or entity. Since that time reports and discussions have appeared in the literature with increasing frequency under the heading "Agranulocytosis," as used by Schultz, or "Agranulocytic Angina," as used in 1923 by Friedmann. Thus, while in 1922 only one article appeared, there were three in 1923, four in 1924, eleven in 1925, eleven in 1926, twenty-eight in 1927, and nearly forty in 1928. These articles have appeared in the order of frequency from the following countries: Germany, Austria, United States, Canada, France, Netherlands, Italy, and Sweden. No cases seem to have been reported in Great Britain.

In surveying the literature I have collected 168 cases reported as agranulocytic angina, and in the bibliography to this article cite the names of the authors who reported the same. No claim is made of an exhaustive analysis and report of literature, for references to many an article were obtained which were inaccessible, particularly foreign contributions. Could these reports be included, the number of published cases would undoubtedly exceed two hundred.

However, not all cases reported as agranulocytic angina can be accepted as such. Thus, as has been previously pointed out, one of Kastlin's cases was an acute arsphenamin poisoning, and Allan's case with thrombocytopenia and purpura hardly fall within the category of agranulocytic angina.

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REPORT OF CASE

P. R., a miner, age seventy, entered the Santa Fe Hospital at Los Angeles November 27, 1928, complaining of burns of both feet sustained almost three months previously while working in hot sand barefooted near Death Valley. Treatment by local physician with ointments and hot compresses had been futile. Previous illness, typhoid fever. No accidents or operations. Habits were moderate. Diathesis was negative for tuberculosis, malignancy, or blood dyscrasias. Further questioning as to symptoms of systemic disease proved futile.

Physical Examination.—A well nourished and developed white male with an apparent vigor and vitality exceptional for his age. Temperature, pulse, and respiration were normal. Blood pressure, 206/120. The eyes showed arcus senilis, but the pupils were regular and reacted to light and accommodation. Teeth were in a poor state of repair, and oral hygiene was poor. No chest pathology. No evidence of cardiac hypertrophy or dysfunction was detected. There was a moderate amount of arteriosclerosis of the peripheral vessels. The abdomen, genito-urinary tract, and skin were negative. No adenopathy. Superficial and deep reflexes reacted normally. Examination of the feet showed the distal phalanx of the fourth right toe missing, a second degree burn on the medial surface of the right third toe, and absence of the nail from the left fifth toe. The skin on both feet was somewhat parched; walking was quite painful.

The laboratory reported a hemoglobin of 100 per cent, a leukocytosis of 23,000 with 82 per cent polymorphonuclears; a urine free from albumin, sugar, casts, or pus; a blood sugar of 93 milligrams, and a negative Wassermann.

Treatment consisted of antipyrexol dressings, potassium iodid, grains 15, three times a day, and Buerger's exercises.

Progress was somewhat slow, but on the whole satisfactory, the temperature remaining normal and the burns improving.

On January 12, 1929, forty-seven days after the patient entered the hospital, he developed a temperature of 102 degrees and complained of a sore throat. Inspection revealed a marked redness and inflammation of the throat with a white, greenish exudate high in the left tonsillar fossa. A complete blood count was done and the following report returned: hemoglobin, 86 per cent; red cells, 5,240,000; leukocytes, 3300, with 100 per cent lymphocytes. The urine contained acetone and diacetic acid. On the sixteenth the white count was repeated. The report was 3000 with 100 per cent lymphocytes. A throat culture was negative for diphtheria and *B. pyocyaneus*. The temperature ranged from 100 to 102 degrees.

By January 18 the exudate, which was fairly well localized to the left tonsil, had become ulcerated and more than triple in size. The gums and left buccal membranes were involved with white patches. The sclera had an icteric tinge. The patient was toxic and in an evident critical condition.

A blood count was done again on the nineteenth, revealing a hemoglobin of 67 per cent, 900 leukocytes with no granular cells seen. The platelet count was 320,000. The blood culture was negative. The patient was now deeply jaundiced and comatose. The temperature dropped to 96.6 degrees, and he expired the same night, eight days after the onset of the acute condition.

Treatment was symptomatic throughout the course of the agranulocytic angina, with gargles, mercurochrome swabs, and antipyretics. Leukocytic extract was administered daily intramuscularly during the last five days. Three-tenths gram of neoarsphenamin was given intravenously the day before the patient's death.

Autopsy was performed by the county coroner, who rendered the following report: "The body was very yellow on exterior. Heart and lungs were negative. Liver and gall bladder and kidneys were not dis-

eased. The spleen was moderately large and firm, with white pinhead-sized spots on capsule. Cause of death: Agranulocytic leukemia associated with ulcerative tonsillitis and pharyngitis; possible contributory factor, second degree burns of feet."

Sections were obtained from the bone marrow of the middle one-third of the femur, the liver, spleen, and kidneys, which had one common denominator: no granular cells were to be found in any section. The bone marrow was yellow and fatty, showing no cellular reaction whatever, and a dearth of granulocytes or their prototypes. The kidneys were quite normal except for cloudy swelling. The liver showed small areas of necrosis with lymphocytic, but no granulocytic infiltration, in addition to cloudy swelling. The spleen showed an exaggerated number of reticulo-endothelial cells in the sinuses, but no polymorphonuclear leukocytes could be found here either.

COMMENT

This case is unique in that it occurred during hospitalization for another ailment, only four similar cases having been reported previously. With one exception, this patient was the oldest of any reported cases afflicted with agranulocytic angina. It is further interesting to note that upon entrance to the hospital the patient possessed a normal mechanism of response to infection, carrying a leukocytosis of 24,000 with a normal percentage of granular cells, thus disproving one theory that agranulocytic angina is due to congenital hypoplasia of the bone marrow with consequent inability to ward off infection.

ETIOLOGY

The exciting cause of this malady is not known. Females are more susceptible than males, the ratio of morbidity being 3.8:1. The majority of cases are middle-aged, between thirty to fifty. The mathematical mean was forty years of age in this series. The youngest patient was a boy four and a half years old; the oldest a man seventy-nine. Season and climate do not appear to exert any influence. Heredity seems to play no part, although Hart reports two cases occurring in sisters. All evidence points against any epidemic or contagious element. One attack apparently does not confer immunity, for a case is on record where the patient recovered from a first attack only to succumb to the second two years later. Generally rundown, weakened conditions, and previous diseases, the most common of which are rheumatism and arthritis, must be considered as predisposing causes.

Many adhere to a bacterial origin. Positive blood cultures were obtained in 12 per cent of cases here reviewed, in the following order of frequency: streptococci (30 per cent), staphylococci (20 per cent), *B. pyocyaneus* (20 per cent), pneumococcus (15 per cent), Friedlander's pneumobacillus (10 per cent), and *B. coli* (5 per cent). *Bacillus pyocyaneus* and *B. staphylococcus aureus* from two patients, injected into rabbits, caused death in two days. *B. pyocyaneus* from another produced a leukopenia in rabbits. But the clinical picture cannot be produced by intraperitoneal injection of whole blood into guinea-pigs; neither will the exudation of the ulceronecrotic lesions of the throat of patients, placed on the tonsils of rabbits, produce the lesion.

Adherents to the theory of bacterial origin believe the syndrome represents an atypical reaction of the hematopoietic system to septicemia, due either to bacteria with a specific affinity and toxicity to the granulocytic system, or to an atrophy or hypoplasia of this organ because of septic infection. This bacterial cause may be nonspecific, or specific: *B. pyocyaneus*, streptococci, or fusospirilli.

Sundry other theories as to pathogenesis exist. Some students attribute the unknown cause of the leukemias to that of agranulocytic angina. Duke considers it a manifestation of aplastic anemia. Aubertin believes the agranulocytosis due to a degeneration of the medulla as the producing center of granular leukocytes, this degeneration in turn being due to some unknown toxin. Friedmann is probably alone in his contention that it is due to an endocrine disturbance. He also suggests that the pathogenicity for the two sexes may differ.

PATHOLOGY

The tissue changes found in agranulocytic angina are quite constant. Indeed, Schultz contends that this is a separate and distinct disease entity, basing this contention on the uniformity of the pathological findings.

There may be only a few superficial ulcers on the tonsils, or there may be extensive, multiple, deep gangrenous lesions involving not only the membranes of the buccal and pharyngeal cavities, but those of the entire gastro-intestinal tract. An ulcerative colitis is also commonly present. Campbell reports a case where ulcerations were found surrounding the anal orifice only, while Murphy describes one patient who presented no ulcers during life. These, however, are the exceptions. The ulcers are usually covered with a grayish white coat, often closely resembling a diphtheritic membrane.

The inflammatory sites wherever found have a similarity of appearance. Microscopically, we will find superficially a necrotic, granular material intermingled with numerous bacteria. Looking deeper, we notice the cell outline intact, but streak-like accumulations of bacteria may be found in the intercellular spaces. The vessels are often thrombotic, containing hyalin, fibrinous material, or clotted blood, in which the absence of leukocytes is striking. Smaller and larger accumulations of lymphocytes and plasma cells may be present in varying numbers, but only rarely, if ever, will we find any granular cells about the ulcers.

The gangrenous pharyngeal process is now generally accepted as being secondary to the disease of the leukopoietic system, the lack of neutrophilic cells causing a deficiency in the tissue resistance. This is quite strikingly confirmed in Bantz's cases, the anamnesis of two of them indicating a considerable fatigue for two weeks, while a pharyngeal process was lacking. Murphy's case further substantiates this view.

Subpleural hemorrhages are not uncommon. Fibrinous exudate may cover the pleura in places, in which dark red, solid, irregular small foci are

present in the lung. Such areas are quite regularly found, especially in the lower lobes, which may also show hypostatic pneumonia. The capillaries of these solidified parts are hyperemic; the alveoli are filled with red blood cells and in places with bacterial masses. Adjacent alveoli contain an albuminous or fibrinous material. The absence of leukocytes in the foci is most striking.

The liver is often slightly enlarged with evidence of cloudy swelling. Microscopically varying degrees of fatty degeneration, multiple focal necrosis, and a proliferation of Kupfer's cells exist.

The spleen also is frequently somewhat swollen. It is generally dark red and firm, rarely soft as in septicemia. The lymph follicles are not prominent on the surface. There is a hyperplasia of the sinus endothelium at the expense of the lymphocytic tissues, the endothelial cells comprising as high as 90 per cent of the entire splenic substance. Cells which give a positive oxydase reaction are not found.

The kidneys commonly show only signs of cloudy swelling, with hyperemic glomeruli, degeneration of the tubular epithelium, and the tubules filled with casts. Occasionally severe kidney damage is found with many bacterial emboli throughout the cortex, but with no evidence of inflammatory changes.

Very striking changes are found in the bone marrow. No cellular response toward the lack of cells is found, as in the leukemias. Instead we find a persistent dearth of cells positive for the oxydase reaction. Erythroblasts and megakaryocytes are present in approximately normal numbers. That this finding is not due to post-mortem, or even agonal changes, was proven by Zadek, Schultz, and Jacobowitz, who removed bone marrow from the sternum during the height of disease which gave the same findings.

SYMPTOMATOLOGY

The onset is usually quite sudden, although it may be very gradual, the prodromata lasting weeks. Malaise, prostration, asthenia, and hyperpyrexia ranging from 101 to 104 degrees, are the common initial symptoms. The fever is maintained throughout the course of the disease with few remissions. Simultaneous with the fever, or a few hours following the same, the patient complains of a sore throat and dysphagia. Inspection of the mouth and pharynx reveals ulceromembranous lesions, not unlike diphtheria in appearance, but with no uniformity as to location, size, or depth. These areas spread with considerable rapidity, often involving the hard and soft palate, gums and tongue, as well as pharynx.

Some have reported a mild cervical adenopathy, but in the majority of cases no enlargement of the lymph glands is found.

About half of the cases develop jaundice, in varying stages of the disease and of varying intensity. I have not found any reported recoveries of patients who have developed jaundice.

The characteristic finding is obtained in the blood count. A striking leukopenia is encountered from the first, commonly increasing from day to

day throughout the course of the disease. The lowest count is reported by Schultz, who could find no leukocytes in one case; the highest count was reported as 10,000. The average lowest count obtained is 1500. The differential count reveals a pronounced decrease in the polymorphonuclear cells. Quite often no granular cells can be found whatsoever. Rarely no neutrophilic cells are encountered, whereas eosinophils may be found in small numbers (one to two per cent). The average percentage of granular cells is five, lymphocytes constituting practically exclusively the cytologic formula. No immature forms of leukocytes are found in true agranulocytic angina. The red cells and hemoglobin are not remarkable, often remaining present in normal proportions throughout. Commonly, however, there is a drop toward the termination of the disease. The thrombocytes also remain unaffected throughout the disease. No hemorrhagic tendencies are encountered.

The disease is usually of short duration. Nine days is the average in this series for those cases which terminated fatally. Two days was the shortest period, thirty days the longest. The duration is much longer in those patients who recovered, thirty-five days being the average.

DIAGNOSIS

The diagnosis is easily established if one bears the condition in mind and calls for a blood count routinely in all cases of sore throat. The hyperpyrexia, the ulcerative buccopharyngeal lesions, the leukopenia with diminution of the granular cells, and the normal platelet count can hardly fail to establish the correct diagnosis in the average case.

In those rare cases where no ulceration of the membranes occur, or where they occur in atypical locations, the diagnosis will have to rest largely on the blood findings alone.

DIFFERENTIAL DIAGNOSIS

1. *Diphtheria* is perhaps most commonly confused with agranulocytic angina. The confusion is the more common because *B. pyocyaneus* is so frequently recovered in cultures from the throat which, in degenerated forms, may closely resemble the Klebs-Loeffler bacillus. Differentiation is readily made by a Gram stain, the *B. pyocyaneus* being Gram-negative, whereas *B. diphtheriae* is Gram-positive. This is not done routinely in city health laboratories, however, and occasionally a practitioner is severely criticized and placed in an awkward position when he has not given diphtheritic antitoxin to a case of agranulocytic angina, and the health authorities report a positive culture. The blood count will decide.

2. *Septicemia* and its modifications frequently offer baffling difficulties in differentiating from agranulocytic angina. Indeed, many students consider this disease but one type of reaction to sepsis, as has been previously pointed out, and numerous cases reported as agranulocytic angina will be found to come under this heading. In these conditions, however, we will generally find a hemorrhagic diathesis, abscesses, primary infec-

tious foci, a positive blood culture, and myeloid proliferation in the bone marrow.

3. *Vincent's angina* causes ulcerations similar to those of agranulocytic angina, but a direct smear from the mouth readily reveals the causative organism, and a normal leukocytic reaction is the rule.

4. *Typhoid fever, influenza, and miliary tuberculosis* infrequently cause necrosis of the pharyngeal membranes, but their course and pathological manifestations should clarify their diagnosis.

5. *Monocytic angina* or infectious mononucleosis generally occurs at an earlier age, is equally distributed between both sexes, is accompanied by a generalized lymphadenopathy and splenomegaly, and the blood picture reveals a leukocytosis with an increase in the percentage of monocytes. Furthermore, the ulcerations, when they occur, are generally confined to the tonsils. There is no jaundice, the course is protracted, and the outlook is favorable.

6. *Aleukemic leukemia* often presents a hemorrhagic diathesis. There is usually a secondary anemia, thrombocytopenia, and a prolonged bleeding time. Tenderness over the lower end of the sternum is frequently elicited, and, finally, autopsy findings reveal leukemic infiltrations in the liver, spleen, lymph nodes, and kidneys.

7. *Hodgkin's disease* will rarely offer any difficulties of differentiation. However, Jaffe reports a case in all respects simulating agranulocytic angina during life, but on autopsy was found to have multiple abdominal glands typical of Hodgkin's. A wrong diagnosis is probably unavoidable in such rare conditions.

8. *Pernicious and aplastic anemia* present a pronounced reduction in red cells and hemoglobin which are not found in agranulocytic angina. The glossitis, achlorhydria, neurological findings and remissions further distinguish Ehrlich's anemia unmistakably.

9. *Toxins* such as arsphenamin, x-rays, benzene, radium, mesothorium, and thorium x, will produce clinical pictures identical with those of agranulocytic angina, and a negative history of exposure to any of these various agents is necessary before a diagnosis of agranulocytic angina can be established.

PROGNOSIS

The outlook is gloomy, but not infaust. Out of the 168 cases in this series, twenty-two, or 13 per cent, recovered, giving a mortality rate of 87 per cent. This is among the lowest figures encountered; generally the mortality rate is given as 93 to 95 per cent.

Jaundice seems an unfavorable sign; I have noticed no report of an icteric patient recovering. A protracted course is favorable; the majority who survive the first fourteen to eighteen days recover.

TREATMENT

There is no known remedy for agranulocytic angina. Most physicians have treated their cases symptomatically. Transfusions and intravenous administration of neoarsphenamin have been given most commonly, but with no greater per-

centage of recoveries than those cases who received no treatment. Good results have been claimed for intravenous administration of guanin hydrochlorid dissolved in 10 per cent hydrochloric acid, but the cure is all but worse than the disease, as the injection is excruciatingly painful.

A ray of hope is seen in the x-ray therapy as used by Friedman. In his article of May 21, 1928, Friedman reviews twenty-nine cases, five of which were treated with roentgen rays and recovered. Only two of the remaining patients recovered. His cases were given one-twentieth of a skin unit surface dose and deep therapy with six millimeters Cu filter over the long bones.

Based on this report, Call and others treated a patient with x-ray, using the following factors: 4 ma., 130 kv., 2 min., 6 mm. aluminum filter, 50 cm. distance. The first treatment was given over the lower extremities and over the throat; the second was given over the upper extremities and one minute was repeated over the femurs. The patient's white count at this time was 640, with 14 per cent polymorphonuclears. Within a few hours after treatment there was a marked increase in the prepolymorphonuclears, a gradual increase in the granular leukocytes and a decrease in the lymphocytes until the blood picture became normal. The authors admit that all these cases might have recovered without the use of irradiation, but felt that its use could do no harm. The prompt improvement in the blood picture and throat manifestations, and the final return to normal in all of the cases so treated indicates strongly that irradiation was responsible for the results.

Cognizance should be taken of the fact, however, that Zikovsy and Zikowsky used irradiation to the spleen and other organs prior to these reports, but without results.

SUMMARY AND CONCLUSIONS

1. History and literature is briefly reviewed and an additional case reported.

2. Agranulocytic angina is characterized by:

(a) Unknown etiology and pathogenesis. "The demonstration of bacteria in the blood is not a proof of an infectious nature of the disease, as bacteria are also frequently found in late stages of leukemia, and their presence is due to invasion of the body throughout areas of necrosis."

(b) Marked predominance in the female sex (3.8 to 1).

(c) Ulceronecrotic lesions, usually most marked on the buccopharyngeal mucosa, without the common mechanisms of defense surrounding same.

(d) Absence of appreciable tumefaction or metaplasia of hematopoietic organs, but a hyperplasia of the reticulo-endothelial system.

(e) Marked leukopenia with considerable diminution or disappearance of granular white cells, with absence of important modifications in number and quality of red cells and platelets.

(f) Alteration in the bone marrow characterized essentially by disappearance of granular cells.

(g) Hyperpyrexia, marked prostration, and commonly an early fatal termination.

3. Essential agranulocytic angina can usually be differentiated by its clinical and pathological symptoms from diseases showing a secondary agranulocytic complex.

4. The one form of treatment under which most patients have recovered is irradiation to the long bones, as used by Friedmann. The development of this form of therapy is worth following.

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REFERENCES*

DISCUSSION

ARTHUR M. HOFFMAN, M. D. (803 Medical Office Building, Los Angeles).—In the year since the patient whom Doctor Kahlstrom so adequately describes died, there have occurred in the city of Los Angeles five deaths and one recovery from agranulocytic angina. Since we have no reason to believe that the disease is any less prevalent in other parts of this country, it behooves everyone to be on the lookout for it. In fact its incidence can be described in the terms of Cabot, used about pernicious anemia, when he said, "The incidence of the disease is a good deal a matter of keenness on the part of the practitioners of any district."

Our desire to detect the disease should be primarily to attempt early treatment, for if diagnosed late, that is, a week or more after the onset of throat symptoms, the alarming mortality rate takes place and the possible effectiveness of the only hopeful measure we now possess is mitigated. X-ray of the long bones late is of no avail. I have seen two patients in the year since Doctor Kahlstrom's patient died, and both were given x-ray therapy only on the day preceding death. If delay in such therapy persists, the procedure will be discarded—possibly too soon for accurate estimate of its true value.

The presence of the agranulocytic blood picture without angina, in general sepsis as described by Blumer, is an interesting development in our knowledge of the subject. Further adequate case reports and studies like the above should in time give us a clearer insight into the mechanism of this aggravating bone-marrow reaction.

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ALBERT SOILAND, M. D. (1407 South Hope Street, Los Angeles).—Our experience in the radiation treatment of agranulocytic angina has been entirely limited to patients who were far advanced in the disease. One patient was first treated about five days after the onset of very acute symptoms. The white count at this time showed 500 cells, 99.5 per cent lymphocytes, and 0.5 per cent granular leukocytes. Roentgen exposure was given over three areas, both femurs and the upper spine, using 200 K. V., 60 centimeters distance, one-half millimeter copper and one millimeter aluminum filter, four ma. through the tube, and two minutes' time. The following day the white count showed 600 cells, with 100 per cent leukocytes. The same areas were again exposed, and the next day the count was 600 cells, with 98 per cent lymphocytes and 2 per cent granular leukocytes. The patient then showed a marked decrease in white cells, and died. This case was practically terminal when first treated, and we do not believe it possible to stimulate blood cell formation in a patient at this stage of the disease.

Two other very advanced patients whom we observed failed to show improvement.

The cases of recovery after radiation, reported by Friedmann, are encouraging; but we believe that if any value is to be obtained from stimulative treatment of the long bones by radiation, this treatment must be given early in the course of the disease.

* The complete list of references will be listed in the reprints. Copies of reprints may be had on request to the author.